Indian Journal of Chemistry
Vol. 37B, August 1998, pp. 819 - 821

Note

Condensed bridgehead nitrogen heterocyclic systems; Synthesis, stereochemistry and antimicrobial activity of 3,4-*cis*-8,8a-tetrahydro-2*H*,7*H*-pyrazolo[3′,4′:4,5]thiazolo[3,2-*b*]-*s* tetrazines

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Received 21 May 1997; accepted (revised)6 November 1998

7-Arylidene-3,3-diethyl-3,4,6,7-tetrahydro-2*H*-thiazolo-[3,2-*b*]-*s*-tetrazin-6-ones **2** have been synthesised in a single step by the condensation of 6,6-diethyl-1,2,4,5-tetrahydro-*s*-tetrazine-3-thione **1** with ethyl chloroacetate and aldehydes in the presence of pyridine and piperidine. Condensation of **2** with hydrazine hydrate in the presence of anhyd. sodium acetate furnishes 8-aryl-3,3-diethyl-3,4-*cis*-8,8a-tetrahydro-2*H*,7*H*-pryazolo[3′,4′:4,5]thiazolo[3,2-*b*]-*s*-tetrazines **3**. The antibacterial and antifungal activities of some of the compounds have also been evaluated.

In continuation of our earlier work on the synthesis of biologically active condensed bridgehead nitrogen heterocyclic systems[1,6] and in view of the reported antimicrobial activity of thiazolo-*s*-tetrazines[7,8], we report herein the synthesis, stereochemistry and antimicrobial activity of 8-aryl-3,3,diethyl-3,4-*cis*-8,8a-tetrahydro-2*H*,7*H*-pyrazolo[3′,4′:4,5]thiazolo-[3,2-*b*]-*s*-tetrazines **3** derived from 6,6-diethyl-1,2,4,5-tetrahydro-*s*-tetrazine-3-thione **1**.

6, 6-Diethyl-1, 2, 4, 5-tetrahydro-*s*-tetrazine-3-thione **1**,obtained by the reaction of 3-pentanone with thiocarbohydrazide following the method of lamon[9], on condensation with aldehydes in the presence of pyridine and piperidine afforded 7-arylidene-3,3-diethyl-3,4,6,7-tetrohydro-2*H*-thiazolo [3,2-*b*]-*s*-tetrazin-6-ones **2** (Scheme I; Table I). The structures **2** were supported by the appearance of a band in the region 1690-1710 cm^{-1} in their IR specta. Condensation of **2** with hydrazine hydrate furnished 8-aryl-3,3-diethyl-3,4-*cis*-8,8a-tetrahydro-2*H*-pyrazolo[3′,4′:4,5]thiazolo[3,2-*b*]-*s*-tetrazines **3** (Scheme I; Table II). Lack of absorption in the IR spectra of **3** in the region 1690-1710 cm^{-1} showed the absence of a carbonyl group, thereby suggesting the cyclic structure for **3**. The structure **3** was further supported by ^1H NMR spectral data *vide* Experimental). The appearance of two doublets *J*=8.8 Hz) at δ 7.52 and 8.44 ppm for C-8a-H and C-8-H in the ^1H NMR spectrum of **3a** (R_1=H; R_2=C1) corroborated the cyclic structure and *cis*-configuration[10].

Antimicrobial activity. The compounds **3a** and **3e** were evaluated for their antimicrobial activity against the gram-positive *Staphylococcus aureus* and gram-negative *Escherichia coli* and *Pseudomonas aeruginosa* bacteria and the fungus *Candida albicans* by neat samples and serial plate dilution method[11].

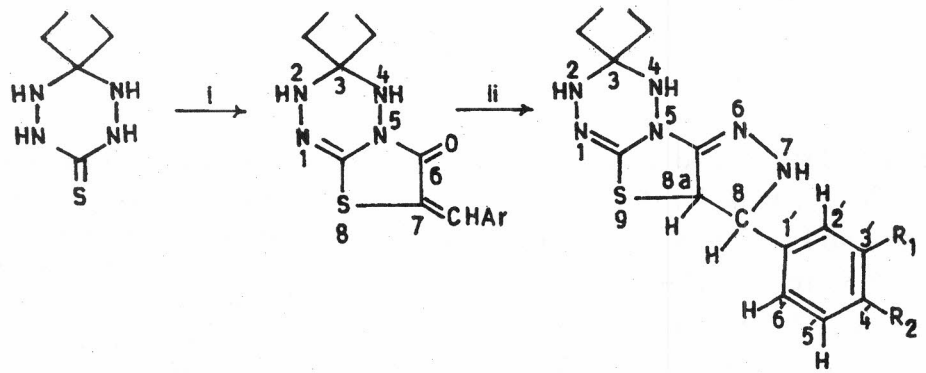
Both the compounds were found to be active against *S.aureus* and *C.albicans* when treated as neat samples and may be used for local application in the form of powder or ointment provided further studies indicate the absence of toxicity following local application.

Experimental Section

General. TLC was run on silica gel-G plates using acetone-benzene (1:3)as irrigant. Melting points are uncorrected. IR (KBr, λ_{max} in cm^{-1}) and ^1H NMR (Chemical shifts in δ, ppm downfield from TMS) spectra were recorded on Beckman IR-20 and Perkin-Elmer (P-32) 90 MHz spectrometers, respectively.

6,6-Diethyl-1,2,4,5-tetrahydro-*s*-tetrazine-3-thione 1. It was prepared in 65% yield by treatment of 3-pentanone with thiocarbohydrazide according to the method of Lamon[9], mp 120 °C. Anal. Calcd for $C_6H_{14}N_4S$: N, 32.18; S, 18.39. Found: N, 32.36; S, 18.67%; IR: 1120 (C=S), 1525 (C-N), 3240, 3472 (N-H).

7-(p-Chlorobenzylidene)-3,3-diethyl-3,4,6,7-tetrahydro-2*H*-thiazolo[3,2-b]-*s*-tetrazin-6(7H)-one 2a (Ar=*p*-C1C_6H_4. A mixture of **1**(0.87g, 0.005 mole), ethyl chloroacetate (0.61g, 0.005 mole) and pyridine (0.45 mL) in anhyd. ethanol



1 2 3

i. $ClCH_2COOEt$, Pyridine, ArCHO, Piperidine; ii. Hydrazine hydrate.

Scheme I

Table I — Characterisation date of 7-arylidene-thiazolo-*s*-tetrazin-6-ones **2** and pyrazolo-thiazolo*s*-tetrazines **3**.

Compd	Ar	R_1	R_2	mp °C	Yield (%)	Mol. Formula	Found (%) (calcd) C	H	N	S
2b	$-C_6H_5$	—	—	152	63	$C_{15}H_{18}N_4SO$	59.32	6.28	18.27	10.87
							(59.60	5.96	18.54	10.59)
2c	*m*-NO_2-C_6H_4	—	—	184	68	$C_{15}H_{17}N_5O_3S$	52.12	5.27	—	9.42
							(51.87	4.90	—	9.22)
2d	*p*-$(CH_3)_2NC_6H_4$	—	—	168	70	$C_{17}H_{23}N_5SO$	58.86	6.34	20.61	9.46
							(59.13	6.66	20.28	9.27)
2e	3,4-$(OCH_3)_2C_6H_3$	—	—	147	56	$C_{17}H_{22}N_4SO_3$	56.14	5.89	15.18	8.48
							(56.35	6.07	15.46	8.83)
3b	—	H	H	180	46	$C_{15}H_{20}N_6S$	57.23	6.18	26.81	9.87
							(56.96	6.32	26.58	10.12)
3c	—	NO_2	H	188	58	$C_{15}H_{19}N_7O_2S$	50.20	5.54	—	9.26
							(49.86	5.26	—	8.86)
3d	—	H	$(CH_3)_2N$	177	52	$C_{17}H_{25}N_7S$	57.38	6.76	27.18	9.27
							(56.82	6.96	27.29	8.91)
3e	—	OCH_3	OCH_3	212	54	$C_{17}H_{24}N_6O_2S$	54.54	6.57	22.68	8.86
							(54.25	6.38	22.34	8.51)

(40ml) was refluxed on a steam-bath for 4 hr. p-Chlorobenzaldehyde (0.68g, 0.005 mole) and piperidine (0.35mL) were then added and the reaction mixture was refluxed further for 4 hr and cooled. The light yellow solid, thus separated, was filtered, washed with water and crystallised from glacial acetic acid to give **2a** as light yellow crystals, mp 168 °C, yield 1.0 g (60%). Anal. Calcd for $C_{15}H_{17}N_4SClO$: C, 53.49; H, 5.05; N, 16.64; S, 9.50. Found: C, 53.81; H, 5.23; N, 16.27; S, 9.76%; IR: 835 (1,4-disubstituted benzene ring), 1510 (C-N), 1585, 1600 (C=C and C=N), 1700 (C=O), 3340 (N-H).

The characterisation data of other thiazolo [3,2-b]-*s*-tetrazin-6(7H)-ones are given in the Table - I.

8-(*P*-Chlorophenyl)-3, 3-diethyl-3,4-*cis*-8, 8a-tetrahydro-2*H*,7*H*-pyrazolo[3′,4′;4,5]thiazolo[3,2-b]-*s*-tetrazine 3a (R_1=H; R_2=Cl). A mixture of **2a** (1.1g, 0.003 mole), hydrazine hydrate (1mL, 0.02

mole), anhyd. sodium acetate (0.49 g, 0.006 mole) and glacial acetic acid (20ml) was heated under reflux on a heating mantle for 6 hr, cooled and poured into cold water. The solid, thus separated, was filtered, washed with water and crystallised from glacial acetic acid as yellow granular crystals, mp. > 250 °C, yield 0.7g (61%). Anal. Calcd for $C_{15}H_{19}N_6SCl$: C, 51.35; H, 5.42; N, 23.96; S, 9.12. Found: C, 51.16; H, 5.32; N, 24.27; S, 9.47%; IR: 820 (1,4-disubstituted benzene ring), 1525 (C-N); ^{1}H NMR (DMSO-d_6; 1.24 (6H,t,methyl protons of ethyl groups), 1.88 (2H, brs, 2XNH, exchangeable with D_2O), 2.20 (4H, q, methylene protons of ethyl groups), 2.92 (1H, s, NH, exchangeable with D_2O), 6.80 [2H,d,J=9 Hz, H-2′ and H-6′), 7.52 [1H, d, J=8.8 Hz, H-8a], 7.72 (2H, d, J=9 Hz, H-3′ and H-5′), 8.44 (1H, d, J=8.8 Hz, H-8).

The characterization data of other pyrazolo-thiazolo-*s*-tetrazines **3** are given in the Table I.

Acknowledgement

The authors are thankful to Prof. Jan K Rozylo of M. Curie-Sklodowska University, Poland for ^{1}H NMR spectra and elemental analyses, to Dr D R Arora of the Department of Microbiology, Medical College, Rohtak for biological screening, to CSIR, New Delhi for the award of senior research fellowship to S K, and to Head of the Chemistry Department, M. D. University, Rohtak for providing laboratory facilities.

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